Kidney International, Vol. 58, Suppl. 76 (2000), pp. S-60–S-65

Adsorption in hemodialysis

JULIO BOTELLA, PAOLO M. GHEZZI, and CARMEN SANZ-MORENO

Department of Nephrology, Puerta de Hierro University Hospital, Madrid, Spain; Department of Nephrology, Ospedale S. Croce, Cuneo, Italy

Adsorption in hemodialysis. The use of sorbents in different blood purification techniques is reviewed. The sorbents used in these therapies are divided into two groups: (*1*) Adsorption occurs fundamentally because of the hydrophobic properties of the sorbents. In this group, the sorbents used in different dialysis techniques are charcoal and nonionic macroporous resins. (*2*) Adsorption occurs by chemical affinity, such as ion exchange resins and chemisorbents. Sorbents were initially used in hemoperfusion, which caused many adverse events; later, with the use of coated charcoal, these undesired effects decreased or disappeared, but the adsorptive properties, water control, and acid-base balance still created problems. For these reasons, the use of sorbents in the treatment of chronic renal failure was almost totally discontinued. Little by little, interest in these substances has reappeared, and at present, they have been used in combination with other blood purification techniques such as hemodialysis, hemofiltration, peritoneal dialysis, and finally, hemodiafiltration. Within the various hemodiafiltration techniques, paired filtration dialysis-charcoal is being used to regenerate the ultrafiltrate, which is used as the replacement fluid. Charcoal regenerates the ultrafiltrate and transforms it into a physiological solution with a normal electrolyte composition, calcium, bicarbonate, and glucose, having eliminated the majority of both middle and large molecule uremic toxins. If regeneration is done properly, this replacement fluid is bacteria and endotoxin free. Studies currently are underway on the adsorption of different inflammatory substances in the ultrafiltrate, which could lead to improvement in the biocompatibility of the system.

According to the "Consensus Conference on Biocompatibility," adsorption is a method for removal of molecules from blood or plasma by attachment to a surface incorporated in a module within an extracorporeal circuit [1]. Sorbents are substances that, because of their physical and chemical characteristics, adsorb on their surface other elements in dissolution. Nephrologists are therefore accustomed to using sorbents in hemodialysis units to purify the urban tap water used to produce dialysis fluid. Active carbon—charcoal—is used in the treatment of this water to adsorb various substances, among which are the chloramines, and also ionic resins are used to eliminate excess of calcium and to avoid hard water syndrome [2]. In medicine, sorbents have been used to rapidly eliminate both industrial and pharmacological exogenous toxins, as well as some endogenous toxins such as bilirubin or porphyrines.

Sorbents can be divided into large categories: (*1*) those that have hydrophobic properties and therefore adsorb the molecules dissolved in the solution in contact with the sorbent, and (*2*) those that eliminate solutes by chemical affinity [3]. Within the first category, hydrophobic sorbents, there are two subgroups: charcoal and nonionic macroporous resin. Charcoal is produced both from biological substances such as coconut shells or peach pits and from nonbiological substances, such as petroleum. The charcoal is activated by controlled oxidation in air, carbon dioxide, or steam. Adsorption into charcoal occurs through its pores, and therefore, its efficiency depends on the total number of pores and their radius. The charcoal may be coated or uncoated. Coating charcoal reduces some of its adverse effects, such as platelet entrapment, but it also reduces its efficiency, since the diffusion of the toxin from the blood to the charcoal is impeded by the thickness of the polymer membrane, which covers it. The nonionic macroporous resins are very similar to charcoal and are microsphere agglomerates, which adsorb the toxins they eliminate in their surface. Polystyrene amberlite is generally used in clinical practice.

The sorbents, which eliminate substances by chemical affinity, are fundamentally ion exchange resins, which exchange one ion for another of the same electrical charge. Some substances, which act by chemical links between the sorbent and the solute, are also considered "chemisorbents." The ingestion of oxy-starch and oxycellulose, for example, eliminates urea and ammonia from the feces.

SORBENTS AND HEMOPERFUSION

Again, according to the definitions of the "Consensus Conference on Biocompatibility," hemoperfusion is the passage of blood across material that adsorbs various solutes or substances [1]. In nephrology, sorbents were

Key words: hemoperfusion, sorbents, biocompatibility, chemisorbents, macroporous resins, ultrafiltrate.

first used by Muirhead and Reid in 1948 [4] and later by Yatzidis in 1964 [5] in hemoperfusion to eliminate uremic toxins. However, the adverse effects, principally platelet depletion, hemolysis, hemorrhage, and hypotension, outweighed the advantages. Although the majority of these adverse effects were solved thanks to the introduction of coated charcoal by Chang in 1966 [6, 7], the isolated use of hemoperfusion for the treatment of uremia has been discontinued. At present, the use of hemoperfusion is an accepted treatment for certain exogenous intoxication (pharmacological or suicidal). Some recent studies implicate a potential benefit derived from sorbents in the management of acute hepatic failure, cirrhotic ascitis, and septic shock [8–12].

SORBENTS AND HEMODIALYSIS

After the failure of hemoperfusion in the treatment of chronic renal failure, sorbents were used in combination and simultaneously with other dialysis methods. Gordon et al in 1969 first described a hemodialysis technique in which the blood system, including the dialyzer, was the usual one, but only 6 L of dialysis fluid were used in the entire session, as the dialysate was regenerated by sorbents [13]. The cartridge containing the sorbents consisted of four compartments: the first with urease, which transformed urea into ammonia; the second with zirconium phosphate, which eliminated ammonia, potassium, calcium, and magnesium; the third compartment, containing hydrated zirconium oxide, which eliminated phosphates; and the final compartment using charcoal, which eliminated a large number of both small and middle molecules. The system, called "Redy," had the advantage of not needing running water nor any type of special installation and, therefore, could be quickly operated anywhere, for example, intensive care units and catastrophe sites, such as earthquakes. It also had various disadvantages. The sodium and acid-base balance were difficult to maintain. Hemodialysis sessions were more expensive, and in the initial models, the cartridge transferred aluminum to the dialysis fluid. Therefore, the system was used less and less frequently and, at present, does not seem to be in use in hemodialysis units.

Sorbents have been combined with hemodialysis by the inclusion of these substances in the dialyzer membrane [14]. In this way, the patients' blood was purified by diffusion as well as by adsorption on passing through the dialyzer. The disadvantage to this method was its short efficiency period, as the sorbent became saturated in the first hour of dialysis and then stopped eliminating the uremic toxins.

Other authors, Stefoni et al [15] and Chang et al [16], modified the dialysis scheme of patients with end-stage renal disease by including a weekly hemoperfusion session. Although the reported results were fairly satisfactory, combined treatments, hemodialysis and hemoperfusion, did not enter routine use.

SORBENTS AND HEMOFILTRATION

The Redy sorbent cartridge was used by Shaldon et al to regenerate the hemofiltration ultrafiltrate, using this regenerated liquid for reinfusion [17]. This study was discontinued because of the appearance of osteomalacia in the patients. Shapiro, Schilb, and Porush also treated four patients for 45 weeks with hemofiltration and regeneration of the ultrafiltrate by sorbents [18]. He had no problems with osteomacia and found that blood aluminum levels decreased.

SORBENTS AND CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

To increase the number of exchanges without increasing dialysis fluid, two authors, Lewin and Maxwell [19] and Roberts et al (abstract; *J Am Soc Nephrol* 5:426, 1994), reported studies regarding the use of Redy system in continuous cyclic peritoneal dialysis. This system regenerated the exchange fluid with sorbents and reused it. The principal drawback to this system was the decrease in the effectiveness of urease caused by the proteins in the peritoneal fluid.

SORBENTS AND HEMODIAFILTRATION

Various techniques of hemodiafiltration were developed to reach "adequate dialysis" [20]. But how can we define this term? The word adequate comes from the Latin term "*adecuare*," which means "to equal." Therefore, adequate dialysis would be that which restores patients' parameters to normal; however, the question is, which parameters? Biochemical, hematological, cardiovascular? A definition that almost all nephrologists can accept is, "adequate dialysis is the one which restores the patients to the most normal length and quality of life possible, which is tolerated well clinically with a minimum of intra- and extra-dialysis problems." This requires not only that the ideal Kt/V must be achieved, but also, considering the existence of small, middle and large molecules, the use of more permeable or high-flux membranes. In addition, proper purification of the wide range of uremic toxins requires maximum diffusion and convection. Finally, biocompatibility must be taken into account, given that if we are not sure what the uremic toxins are, and we therefore do not know precisely which biochemical parameters should be restored to their normal level, "adequate dialysis" at least should not alter the patient's status even more. This means that it should be as biocompatible as possible, since biocompatibility is defined as "the ability of a material, device or system

to perform without a clinically significant host response in a specific application" [21]. Therefore, adequate dialysis should use biocompatible materials, avoid backfiltration, and use the purest possible dialysis and reinfusion fluids.

In 1978, Leber, Wizemann, and Goubeau described the technique of hemodiafiltration that through the years has given rise to its different modalities: high-flux hemodiafiltration, acetate free hemodiafiltration, etc. [22]. However, all of them have at least one drawback: As diffusion and convection take place simultaneously, both phenomena interfere with each other and decrease their respective efficiency. (*1*) Membrane diffusion decreases throughout hemodialysis or hemodiafiltration because of the formation of a pseudo membrane or "protein cake," which is produced as a consequence of convection and transmembrane pressure [23]. (*2*) The following mathematical reasoning explains the decrease in convective clearance when convection and diffusion coexist simultaneously:

Clearance of hemodiafiltration: $K_{hdf} = K_{uf} + K_d$
Clearance of ultrafiltration or convection: $K_{uf} = Q_{uf} (C_o/C_i)$
However, $C_o < C_i$, and therefore $C_o/C_i < 1.0$
Then, $K_{uf} < Q_{uf}$
Consequently, $[K_d + K_{uf}] < ([K_d] + [K_{uf}])$.

where K_{hdf} is the clearance of hemodiafiltration; K_{uf} is clearance of ultrafiltration; K_d is clearance of diffusion; Q_{uf} is ultrafiltration flow; C_o is concentration out; C_i is concentration in; [] is one chamber only; ([] + []) is one dialyzer with two chambers.

This means that the sum of the two clearances, when these occur simultaneously in the same dialyzer, is less than the sum of both when they occur in different dialyzers.

Ghezzi et al first described the paired filtration dialysis (PFD) technique [24, 25]. In this hemodiafiltration mode, the hemodialysis filter is composed of two dialyzers in series (Fig. 1). The first chamber is a hemofilter for convection only, while the second dialyzer is a made of a low-flux membrane (polysulfone or synthetically modified cellulose) and is where diffusion occurs. In addition, the ultrafiltration necessary to eliminate interdialysis weight gain occurs in the diffusive dialyzer. Therefore, this technique physically separates convection from diffusion, thus leading to two main results: (*1*) the continuous availability of pure ultrafiltrate during the whole duration of the session, and (*2*) the abrogation of backfiltration of dialyate. The end result is the possibility to regenerate the ultrafiltrate and to improve the system's overall biocompatibility. The use, efficiency, and tolerance to this technique have been proven [26]. However, this technique, as any hemodiafiltration, has various drawbacks: Buffer and calcium are lost in the ultrafiltrate and, as a consequence, the acid-base balance and the Ca/P balance become difficult. Eight to 10 L of exogenous replacement fluid must be used. The technology is not simple, as it uses two synchronized pumps to produce the ultrafiltrate and reinfusion at the same time. For these reasons, a regeneration of the ultrafiltrate through sorbents and its use as replacement fluid were suggested [27]. This technique was originally named PFD-charcoal.

This technique uses the same two chamber dialyzer as PFD, but the ultrafiltrate is passed through a charcoal cartridge and reinfused into the patient's bloodline in between the two dialyzers. It is important to note that the production of the ultrafiltrate and infusion of the replacement fluid can be done with a single pump, thereby simplifying the process. Different types of coated charcoal (hydrogel acrylic and cellulose) were tried, but both types of coated charcoal showed deficient adsorption of both middle and large molecules. Figure 2 shows the concentration of β_2-microglobulin (β_2m) in the ultrafiltrate after passing through the cartridge throughout a PFD-charcoal session. However, when the uncoated charcoal was used, we could observe that β_2m did not appear in the regenerated ultrafiltrate. Therefore, a new type of uncoated charcoal was chosen to regenerate the ultrafiltrate (BAC MU-AZ; Kureha Chemical Industry Co., Ltd., Tokyo, Japan) [28]. This was possible since uncoated charcoal, highly incompatible in direct contact with blood, could be placed in the ultrafiltrate.

Regarding the amount of charcoal to be used in the cartridges, we observed that 85 g of uncoated charcoal was sufficient to maintain an ultrafiltrate free of small and middle molecules (creatinine and vitamin B_{12}), but the β_2m progressively saturated the charcoal. However, by increasing the amount of charcoal to 130 g, complete adsorption of the β_2m in the ultrafiltrate occurred throughout the entire session (Fig. 3). The next step was to be sure the electrolytes and glucose were not adsorbed, thereby making the ultrafiltrate a physiological fluid, with the proper osmolarity, calcium, bicarbonate, and glucose. Figure 4 shows that the concentration of bicarbonate and calcium in the regenerated ultrafiltrate was maintained throughout the session.

Following these in vitro and ex vivo studies, clinical studies were performed [29, 30]. The multicenter study by De Francisco et al, which included 33 chronic uremic patients showed that: (*1*) there was good clinical tolerance; (*2*) aluminum concentrations in the regenerated ultrafiltrate were always within the upper limits of AAMI standards; (*3*) bacteriological studies and measurements of ultrafiltered endotoxins showed that the regenerated ultrafiltrate was bacteria and endotoxin free, thus meeting the pharmacopeia requirements for intravenous injection; (*4*) patients' biochemical parameters, as well as Kt/V and protein catabolic rate, were not significantly altered; (*5*) the bicarbonate balance improved, and finally; and (*6*) there was a significant decrease in serum

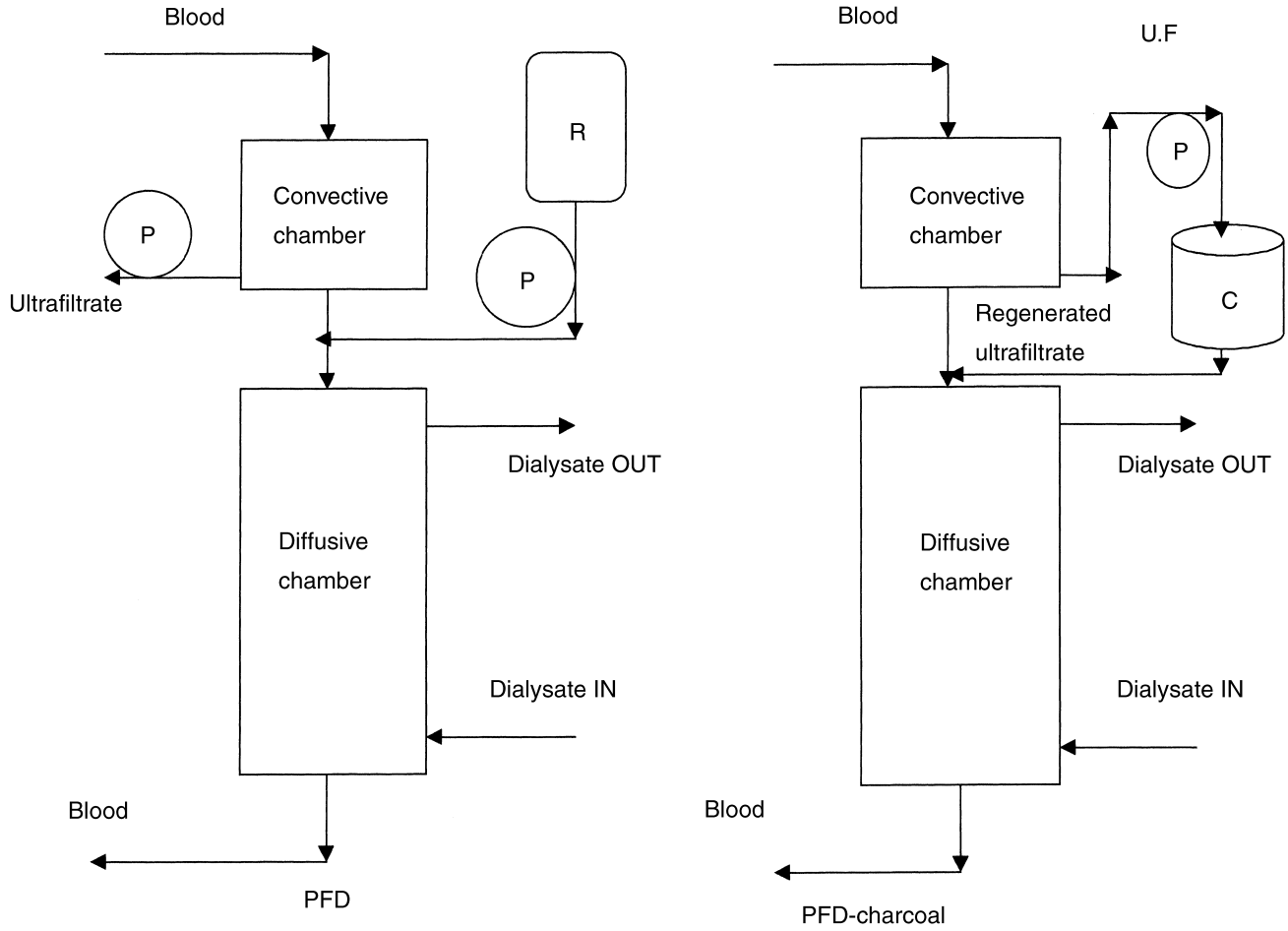

Fig. 1. Schematic drawing of the paired filtration dialysis (PFD) and PFD-charcoal techniques. Abbreviations are: UF, ultrafiltrate; P, pump; R, reinfusion fluid; D, dialysate; DF, dialysis fluid; and C, charcoal.

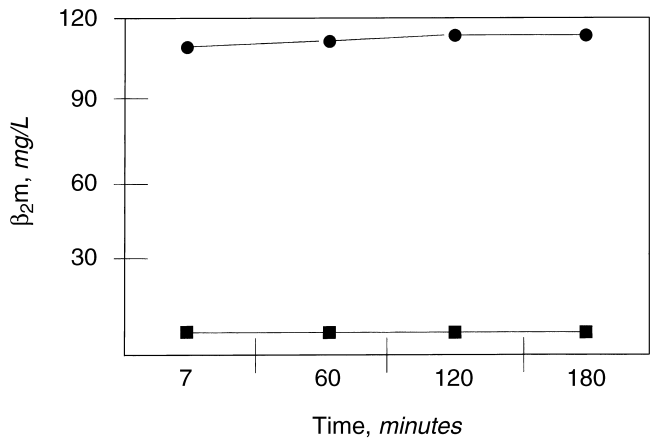

Fig. 2. Quantitative ex vivo studies on the removal of β_2m (mg/L) from ultrafiltrate after passage through charcoal: Effect of coating. β_2m was determined using a highly sensitive radioimmunoassay (Eiken Chemical Co., Ltd., Tokyo, Japan). Symbols are: (●) coated; (■) uncoated.

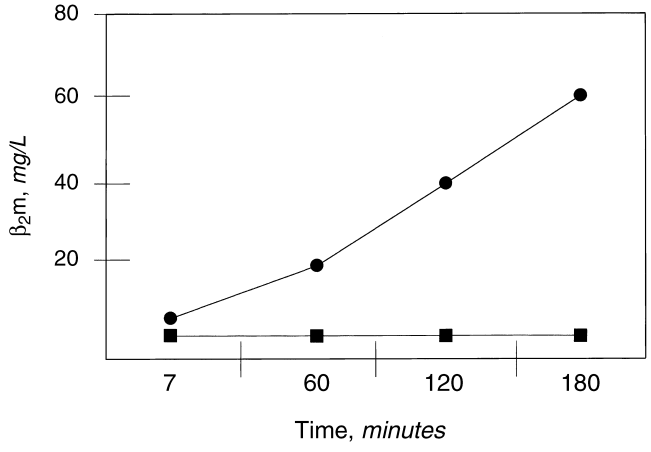

Fig. 3. Quantitative ex vivo studies on the removal of β_2m (mg/L) from ultrafiltrate after passage through charcoal: Definition of the amount of charcoal needed for complete removal. Symbols are: (●) coated, 85 g; (■) coated, 130 g.

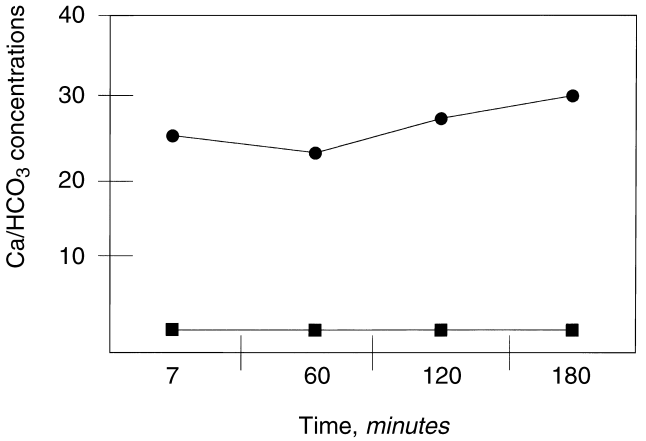

Fig. 4. Bicarbonate (mmol/L; ●) and calcium (mg/L; ■) concentrations in the regenerated ultrafiltrate. Concomitant infusion of bicarbonate and calcium at physiological concentrations could be observed to occur in the regenerated ultrafiltrate. Bicarbonates and calcium were detected using ion-selective assays (Ion Selective, Clark, Severinghouse Electrodes, Stat Profile; Nova Biochemical, Waltham, MA, USA).

values of β_2m at 6 months, which became even greater after 12 months of treatment [30].

SORBENTS, HEMODIAFILTRATION, AND SOME QUESTIONS

Uremic syndrome and its treatment are a source of innumerable questions to be answered, and the use of sorbents in hemodiafiltration is no exception. Among the many questions raised by these therapeutic procedures, two aspects are still unsolved.

First, in the different hemodiafiltration techniques in which the ultrafiltrate is discharged, a series of substances that are beneficial to the organism is eliminated. Are these substances also eliminated (adsorbed) in hemodiafiltration with regeneration through sorbents? For example, are the hydrosoluble vitamins (for example, vitamin C) adsorbed [31]? Vitamin C is an antioxidant. Its loss during hemodialysis could be responsible for the imbalance between pro-oxidants and anti-oxidants, thus leading to unrestrained oxidative stress and the accumulation of advanced glycosylation end products [32]. We also know that nearly all the amino acids are present in the ultrafiltrate, which is not a quantitatively important factor in conventional hemodialysis, but could be a problem in hemodiafiltration and hemodiafiltration [33, 34]. The charcoal only adsorbed seven amino acids (lysine, methionine, histidine, phenylalanine, arginine, tryptophan, and tyrosine), returning the rest of the amino acids to the patient in the regenerated ultrafiltrate [35].

Second, do the sorbents influence the biocompatibility of the system? De Francisco et al's multicenter study showed a statistically significant decrease in β_2m. However, the authors comment that the β_2m extracted with this technique, either by diffusion or convection, cannot explain this decrease. One of the possible explanations the authors offer for this decrease is that PFD-charcoal improves biocompatibility, either because there is no backfiltration or for other reasons. These other reasons may include the possible existence of proinflammatory factors (cytokines, complement factors, tumor necrosis factor-α, interleukin-1, and interleukin-8), which are adsorbed by the charcoal, although it is important to note that charcoal is not the best sorbent for these inflammatory factors. The use of nonionic macroporous resins is more efficient [36].

Reprint requests to Julio Botella, M.D., Artesa de Segre, 3-C, 5-B, Madrid 28035, Spain.
E-mail: jbotella@es.packardbell.org

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